REMARKS

Claims 2-7, 10-24, 29, and 32-39 are pending in the application and claims 17-24 and 32-39 are withdrawn from consideration. The Examiner has withdrawn claims 32-39 from consideration as directed to a non-elected invention. Applicants assert that claims 32-39 are appropriately examined in the instant application as these claims are directed to the elected invention. In response to a restriction requirement issued at the commencement of examination, Applicants elected to pursue claims drawn to a method of delivering a substance into skin (Office Action mailed 4/26/02; pursuant to a telephonic interview with Applicants' representatives on April 2, 2002, a provisional election was made to prosecute claims directed to a method of delivering a substance into skin). Claims 25-30 were then added as part of the elected subject matter (Amendment dated October 28, 2002) and were examined. Subsequently the Examiner restricted the claims to any one of claims 29-31. In an effort to expedite prosecution Applicants elected to pursue claim 29 for prosecution on the merits. Claim 29 is directed to methods of intradermal delivery of a drug and at no time during prosecution been limited in scope to delivery of hormones, let alone PTH and insulin. Applicants therefore request that claims 32-39 be examined in the instant application. Applicants respectfully request that the remarks made herein be entered into the record of the instant application.

1. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, AS FAILING TO COMPLY WITH THE WRITTEN DESCRIPTION REQUIREMENT, SHOULD BE WITHDRAWN.

Claims 29, 2-5, and 10-16 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The rejected claims relate to methods for administration of a drug to the intradermal compartment so that the drug is

distributed systemically exhibiting a pharmacokinetic ("PK") profile similar to subcutaneous delivery of the drug, but with higher maximum plasma concentration (Cmax) and a higher bioavailability.

Applicants contend that the specification as a whole, including the working examples and the figures, as originally filed fully support the claimed invention. Drawings may provide a written description of an invention as required by 35 U.S.C. § 112 (M.P.E.P. § 2163, II.A.). For example, Figure 4 of the instant application as filed is a plot comparing plasma levels of insulin delivered intradermally versus subcutaneously, from the time of delivery until plasma levels of drug are virtually non-existent. Figure 4 demonstrates the delivery of a substance to the intradermal compartment of a subject's skin in accord with the claimed methods can result in a higher Cmax and bioavailability is higher when delivered intradermally as compared to subcutaneously. Bioavailability is measured by calculating the "**a**rea **u**nder **c**urve" (AUC). In other words, the area of the PK profile spanning over the time points is calculated. Thus, as indicated by the AUC measurements in Figure 4, the overall bioavailability of insulin is higher for ID delivery compared to SC delivery. The Merck Manual of Diagnosis and Therapy (17^{th} ed)(1999)("the Merck Manual") clearly states that bioavailability determinations based on the peak plasma concentration (Cmax) can be misleading and that bioavailability determination based on peak time (Tmax) is often not a good statistical measure. The Merck Manual also clearly states that "the most reliable measure of bioavailability is AUC" (see, p. 2560 of the Merck Manual).

The specification as filed clearly supports the claimed invention and the rejection of claims 29, 2-5, and 10-16 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement should be withdrawn.

2. **THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF ENABLEMENT, SHOULD BE WITHDRAWN.**

Claims 29, 2-5, and 10-16 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner contends that the specification is not enabling for the full scope of the claimed invention. Applicants respectfully disagree and submit that the Examiner has erroneously relied on "unpredictability" of biologic systems and focused only on the working examples presented in the specification, and not the teachings of the specification as a whole.

The Examiner's contention of unpredictability is misplaced and controverted by the evidence of record. In support of their position, Applicants have previously submitted a Rule 132 Declaration by Dr. Pettis ("the Pettis Declaration") which accompanied a Supplemental Amendment filed January 6, 2005, and a Rule 132 Declaration by Dr. Kasting ("the Kasting Declaration") which accompanied an Amendment filed October 7, 2005. The Pettis Declaration points to evidence demonstrating that the intradermal delivery of insulin following the teachings of the specification results in the claimed PK profile, *i.e.,* a higher maximum plasma concentration (Cmax) and a higher bioavailability (AUC) as compared to subcutaneous delivery (*see,* the Pettis Declaration at ¶ 9). The Pettis Declaration further points to evidence that delivery of PTH via the methods provided in the instant specification results in the claimed PK profile – an increased Cmax and an increased AUC relative to subcutaneous delivery (*see,* the Pettis Declaration, ¶ 10). The Pettis Declaration further points to evidence that intradermal delivery of low molecular weight heparin, Fragmin®, following the teachings of the specification results in the claimed PK profile – increased Cmax and a higher AUC relative to subcutaneous delivery (*see,* the Pettis Declaration at ¶ 14).

Further evidence that the full scope of the claimed invention is enabled by the instant application can be found in a later filed related application serial No. 10/028,989 (Publication No. US 2002/015453, published October 24, 2002, "the '989 application"). Figure 3 of the '989 application demonstrates that intradermal delivery of LisPro, a fast acting insulin, following the teachings of the specification results in an enhanced Cmax and AUC relative to subcutaneous delivery. Figure 6 of the '989 application demonstrates that intradermal delivery of granulocyte colony stimulating factor (Neupogen) following the teachings of the specification results in an enhanced Cmax and AUC relative to subcutaneous delivery.

Applicants have provided evidence in this record that in addition to the insulin and PTH examples in the instant application – low molecular weight heparin (Fragmin®), fast acting insulin (LisPro), and granulocyte colony stimulating factor (Neupogen) can all be delivered intradermally following the teaching of the instant application to achieve the claimed PK profile. Thus, the evidence of record clearly shows that the method of the invention works with at least five different species. In further support, Applicants have provided the Kasting Declaration, where Dr. Kasting, one skilled in the art who reviewed the instant application concluded that it provides sufficient guidance to allow one skilled in the art to practice the claimed method to achieve the claimed PK profile for any drug of choice (*see,* the Kasting Declaration, ¶ 16). Dr. Kasting carefully reviewed the specification and cited to the specific disclosures and teachings that support the basis for his conclusion that the invention could be practiced without undue experimentation. (*See*, Kasting Declaration at ¶¶ 7-15).

In sum, Applicants have provided evidence that the claimed invention is enabled for at least five different species. Applicants have also submitted a declaration of one skilled in the art that after careful review concludes that the specification enables the successful practice of the invention without undue experimentation. The Examiner's rejection appears

to be based on unsupported opinions. If the Examiner is aware of any evidence to the contrary, and to the extent this rejection is based on facts within his personal knowledge, Applicants request that the Examiner provide an affidavit pursuant to the provisions of 37 CFR §1.104(d)(2).

Further to the remarks presented herein, Applicants reiterate the statements and arguments presented in their response filed on October 7, 2005 supporting that the instant specification provides sufficient teaching to enable one of skill in the art to make and use the claimed invention without undue experimentation; thus, the rejection should be withdrawn.

3. THE REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 29, 2-7, and 10-19 are rejected under 35 U.S.C. §103(a) as obvious over Gross in view of US Patent No. 3,814,097 to Ganderton *et al.* ("Ganderton") and/or Autret et al., 1991, Therapie; 46:5-8 ("Autret"), Puri *et al.*, 2000, *Vaccine*, 18: 2600-12 ("Puri"), U.S. Patent No. 6,056,716 to D'Antonio ("D'Antonio"), U.S. Patent No. 6,007,821 to Srivastava ("Srivastava") and The Merck Manual of Diagnosis and Therapy (7^{th} ed.) (1999).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation either in the prior art references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. §2143. A finding of obviousness simply cannot be supported because the combination of references fail to teach or suggest all the claim limitations.

First, the claims require the insertion of a needle into the intradermal compartment of the skin such that the needle's outlet depth and exposed height of the outlet of the needle are

located *within* the intradermal compartment and wherein the outlet has an exposed height of about 0 to 1 mm. This claim limitation is not described nor is it suggested by any of the references. There is no disclosure in Gross as to the height of the outlet, or whether the outlet is located within the intradermal compartment. The Examiner erroneously contends that Gross discloses the use of a single needle with an outlet at a depth of 250um to 2mm. However, Gross is completely silent on to this point.[1] The Examiner is inappropriately reading claim limitations into the prior art reference. Ganderton is equally silent as to an outlet depth. To clarify, the device of Ganderton consists of a permeable pad studded with spikes designed to puncture the stratum corneum of the skin to improve skin permeability, thus at best achieving topical delivery. Drug is applied on top of the pad and when the pad is applied to the skin, the spikes puncture the outer layer of the skin and the drug subsequently diffuses onto the punctured skin. The drug is not actually delivered through the spikes of the device, let alone at a depth required for intradermal delivery. Diffusion of a drug applied topically through punctured stratum corneum is not achieved through a needle having a specified outlet height or inserted at a specified depth within the skin. Likewise, Autret, Puri, D'Antonio, and Srivastiva are each silent as to this claim limitation.

The claims further require that as a result of the claimed delivery method the drug is distributed systemically and exhibits a pharmacokinetic profile similar to subcutaneous delivery, but with a higher maximum plasma concentration and a higher bioavailability. This

[1] A careful reading of the cited sections in Gross and the reference as a whole indicates that no disclosure relating to the height and depth of the needle outlet and the need for their placement within the ID compartment can be found in Gross. As evidenced by Dr. Kasting's Declaration (which accompanied the Amendment filed October 7, 2005), Gross' specification fails to provide guidance on how to target the ID compartment using a needle having an exposed height of 0 to 1 mm so that the needle penetrates the ID compartment and the needle's outlet depth and exposed height of the outlet are located within the ID compartment, as required by the claimed invention. The Examiner has thus improperly attributed disparate teachings from the Applicant's own disclosure into the prior art.

claim limitation is not described nor is it suggested by any of the references. The Examiner takes the position that the claim limitation is not explicitly taught by Gross, rather it is an inherent result of practicing Gross. The Examiner's attention is again invited to the Second Pettis Declaration that was submitted with the Applicants' response filed October 7, 2005. In particular, the Examiner's attention is invited to ¶10 of the Second Pettis Declaration which evidences that administration of a substance to the intradermal compartment does not always result in an enhanced pharmacokinetic profile when compared to subcutaneous delivery. In fact, ¶¶10-11 of the Second Pettis Declaration evidences that *none* of the pharmacokinetic parameters were enhanced as compared to subcutaneous delivery. Thus, demonstrating that, even assuming *arguendo* that Gross does describe intradermal delivery of a substance, such a delivery would not necessarily result in a higher plasma concentration and a higher bioavailability.

The Examiner contends that to the extent Gross does not inherently achieve the claimed pharmacokinetic profile -- this missing element is supplied by Autret, Puri, D'Antonio, Srivastava and the Merck Manual. Applicants respectfully disagree. Autret, *by the authors' own conclusion* and teaching reports that there is no difference in bioavailability when comparing intradermal and subcutaneous delivery (see Autret at p. 10 of the translation). Puri, D'Antonio and Srivastava relate to vaccine delivery and do not relate to drug delivery - - the efficacy of vaccines is not measured using PK parameters, thus, these references can not supply the missing pharmacokinetic profile.

Thus, as the references alone or in combination fail to teach or suggest all the claimed elements, a finding of obviousness simply cannot be supported.

Further to the remarks presented herein, Applicants reiterate the statements and arguments presented in their response filed on October 7, 2005 as to the patentability of the

pending claims in view of the prior art, in particular, the combination of references cited by the Examiner.

4. **THE DOUBLE PATENTING REJECTIONS SHOULD BE WITHDRAWN**

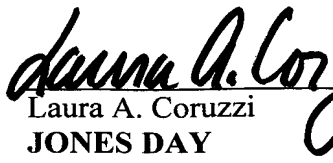
Claims 29, 2-7, and 10-16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over certain claims of copending Application Nos. 10/868,482; 10/867,908; 10/487,485; 11/004,780; 11/004,778; 10/841,992; 10/803,735; 10/650,039; 10/429,973; 09/893,746; 10/028,988; and 10/028,989. Given that the rejection is a provisional rejection, Applicants request that the rejection be held in abeyance until the claimed subject matter is deemed allowable. At that time, Applicants request that the rejection be withdrawn and that the instant application be permitted to issue without need of a terminal disclaimer. Given that each of the applications cited in the nonstatutory obviousness-type double patenting rejection are still pending and are filed later in time than the instant application, it is proper once the instant application is deemed allowable that it be allowed to issue without the need of a terminal disclaimer *See,* M.P.E.P. §804, I.B.1

CONCLUSION

The Applicant respectfully requests that the Examiner enter the amendments and consider the remarks made herein. Withdrawal of all rejections, and an allowance is earnestly sought. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

Respectfully submitted,

Date: August 23, 2006



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